QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

TECHNICAL FIELD

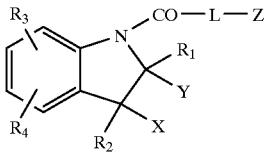
This invention relates to medicines, particularly quinuclidine derivatives or their salts, or quaternary ammonium salts having muscarinic receptor antagonistic activities and also to pharmaceutical compositions containing such compounds.

BACKGROUND ART

Studies have been made on the muscarinic receptor, and it is known that compounds having muscarinic receptor antagonistic activities cause bronchodilation, suppression of gastrointestinal motility, suppression of acid secretion, dry mouth, mydriasis, suppression of bladder contraction, hypohidrosis, tachycardia, or the like. It is known that the muscarinic receptor includes at least three subtypes. The M_1 receptor mainly exists in the brain or the like, the M_2 receptor in the heart or the like, and the M_3 receptor in the smooth muscles or gland tissues.

A number of such compounds having muscarinic receptor antagonistic activities are hitherto known and, for example, atropine is a typical example ("The MERCK INDEX, ELEVENTH EDITION", p. 138). However, atropine antagonizes the M_1, M_2 and M_3 receptors non-selectively, so that it is difficult to use it for the treatment of a specific disease. In recent years, according to the progress of the studies on the subtypes of the muscarinic receptor, compounds having selective antagonistic activities against the M_1, M_2 or M_3 receptor have been investigated (an unexamined published British Patent Application No. 2,249,093, an unexamined published Japanese Patent Application (kokai) 1-131145, and an unexamined published Japanese Patent Application (kokai) 3-133980). There is a demand for a compound having selective antagonistic activity against muscarinic M_3 receptor among these three subtypes and is free from the cardiac side effects resulting from the M_2 receptor.

The compound represented by the following general formula is described in an unexamined published Japanese Patent Application (kokai) 62-252764.

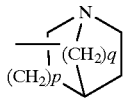


(wherein L represents NH or O;

X and Y each independently represents a hydrogen atom or a C_{1-6} alkyl group or they may be combined together to form a bond;

R_1 and R_2 each independently represents a hydrogen atom, a C_{1-6} alkyl group . . . (omission) . . . ;

R_3 and R_4 each independently represents a hydrogen atom, a halogen atom, CF_3, a C_{1-6} alkyl group . . . (omission) . . . , a phenyl group, an amino group which may optionally be N-substituted by one or two groups selected from phenyl, C_{1-6} alkyl groups or may optionally be N-disubstituted by C_{6-8} polyethylene . . . (omission) . . . ;



p is 1 or 2; and q is 1–3.

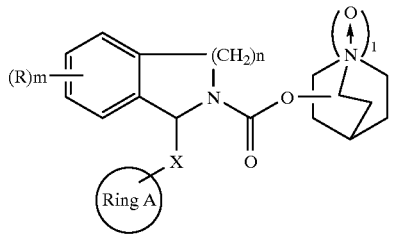
The compound described in the above patent literature is disclosed as a 5-HT antagonist and no disclosure about the muscarinic receptor antagonistic activity is found. The above compound is clearly distinguished from the compound according to the present invention in pharmacological effects.

DISCLOSURE OF THE INVENTION

The inventors of the present application have carried out extensive studies on compounds having the above-described muscarinic M_3 receptor antagonistic activities. As a result, we created novel quinuclidine derivatives having a basic skeleton different from that of the conventional compound, and found that such compounds have excellent selective antagonistic activity against muscarinic M_3 receptor, resulting in the completion of the present invention.

Thus, the compounds of the present invention relate to quinuclidine derivatives represented by the following general formula (I); their salts, or quaternary ammonium salts; pharmaceutical compositions comprising said compounds or salts thereof and pharmaceutically acceptable carriers, particularly to muscarinic M_3 receptor antagonists.

(I)



(symbols in the formula have the following meanings:

Ring A: an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, wherein said ring may be substituted by an optional substituent;

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

l: 0 or 1,

m: 0 or an integer of 1 to 3, and